CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER

20-297/S-009

Administrative Documents

Confidential

GlaxoSmithKline

Coreg® (carvedilol) Tablets

SKF-105517

Item 13/14 Patent Information/Patent Certification

Catherine K. Clark

U.S. Regulatory Affairs

SB Document Number: SKF-105517/RSD-101T35/1

Item 13/14 - Patent Information/Patent Certification

The following patent information is being submitted pursuant to 21 C.F.R. 314.53.

Patent No.	Expiration Date	Type of Patent	Patent Owner	Representative of Patent Owner
4,503,067	March 5, 2007	Drug	Boehringer Mannheim GmbH	Mary E. McCarthy Corporate Intellectual Property GlaxoSmithKline 709 Swedeland Road Mail Code UW2220 King of Prussia, PA 19406

The undersigned declares that U.S. Patient Number 4,503,067 covers the drug Coreg® (carvedilol). This product is currently approved under Section 505 of the Federal Food, Drug and Cosmetic Act.

Catherine K. Clark

Director, U.S. Regulatory Affairs

EXCLUSIVITY SUMMARY for NDA # 20-297 SUPPL # 009

Trade Name Coreg Generic Name carvedilol

Applicant Name GlaxoSmithKline HFD- 110

Approval Date March 27, 2003

PART I: IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, but only for certain supplements. Complete Parts II and III of this Exclusivity Summary only if you answer "YES" to one or more of the following questions about the submission.

   a) Is it an original NDA? YES/___/ NO /_X__/

   b) Is it an effectiveness supplement? YES /_X__/ NO /___/

      If yes, what type(SE1, SE2, etc.)? SE1

   c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "NO.")

      YES /_X__/ NO /___/

      If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

      If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES /___/ NO /_X__/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /___/ NO /_X__/

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule previously been approved by FDA for the same use? (Rx to OTC Switches should be answered No - Please indicate as such).

YES /___/ NO /_X__/

If yes, NDA # _____ Drug Name

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X__/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9 (even if a study was required for the upgrade).

PART II: FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES
(Answer either #1 or #2, as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /_X__/ NO /__/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA # 20-297 Coreg (carvedilol)

NDA #

NDA #

2. Combination product.

If the product contains more than one active moiety (as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA #

NDA #

NDA #

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9. IF "YES," GO TO PART III.

PART III: <u>THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS</u>

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2, was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

   YES /_X__/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON Page 9.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis

for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

For the purposes of this section, studies comparing two products with the same ingredient(s) are considered to be bioavailability studies.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__X_/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval **AND GO DIRECTLY TO SIGNATURE BLOCK ON Page 9:**

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /_X__/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Investigation #1, Study # CAPRICORN

Investigation #2, Study #

Investigation #3, Study #

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

(a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1	YES /___/	NO /_X__/
Investigation #2	YES /___/	NO /___/
Investigation #3	YES /___/	NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

NDA # _____ Study #
NDA # _____ Study #
NDA # _____ Study #

(b) For each investigation identified as "essential to the approval," does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /_X__/

Investigation #2 YES /___/ NO /___/

Investigation #3 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify the NDA in which a similar investigation was relied on:

NDA # _____ Study #

NDA # _____ Study #

NDA # _____ Study #

(c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

Investigation #__, Study # CAPRICORN

Investigation #__, Study #

Investigation #__, Study #

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

(a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # [redacted] YES /_X__/ NO /___/ Explain:

Investigation #2

IND # _____ YES /___/ NO /___/ Explain:

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study?

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

_____

_____
Signature of Preparer Date
Title: Regulatory Health Project Manager

Signature of Office or Division Director Date

cc:
Archival NDA 20-297/S-009
HFD-110 /Division File
HFD-110 /Melissa Robb, RHPM
HFD-093/Mary Ann Holovac
HFD-104/PEDS/T.Crescenzi

Form OGD-011347
Revised 8/7/95; edited 8/8/95; revised 8/25/98, edited 3/6/00

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/s/

Robert Temple
3/27/03 11:54:29 AM

PEDIATRIC PAGE

(Complete for all APPROVED original applications and efficacy supplements)

NDA/BLA # : 20-297 **Supplement Type (e.g. SE5):** SE1 **Supplement Number:** 009

Stamp Date: September 27, 2002 **Action Date:** March 27, 2003

HFD 110 **Trade and generic names/dosage form:** Coreg (carvedilol) Tablets

Applicant: GlaxoSmithKline **Therapeutic Class:**

Indication(s) previously approved: Hypertension and Mild to Severe Heart Failure

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 1

Indication #1: Left Ventricular Dysfunction following Myocardial Infarction

Is there a full waiver for this indication (check one)?

X **Yes: Please proceed to Section A.**

☐ **No: Please check all that apply:** ____Partial Waiver ____Deferred ____Completed
NOTE: More than one may apply .
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
X **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for partial waiver:

☐ **Products in this class for this indication have been studied/labeled for pediatric population**
☐ **Disease/condition does not exist in children**
☐ **Too few children with disease to study**
☐ **There are safety concerns**
☐ **Adult studies ready for approval**
☐ **Formulation needed**
☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ kg_____ mo._____ yr._____ Tanner Stage_____
Max_____ kg_____ mo._____ yr._____ Tanner Stage_____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

Melissa Robb
Regulatory Health Project Manager

cc: NDA 20-297/S-009
HFD-950/ Terrie Crescenzi
HFD-960/ Grace Carmouze
(revised 9-24-02)

FOR QUESTIONS ON COMPLETING THIS FORM CONTACT, PEDIATRIC TEAM, HFD-960
301-594-7337

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/s/

Melissa Robb
3/27/03 12:58:48 PM

Item 16 Debarment Statement Certification

Pursuant to Section 306(K)(1) of the Federal Food, Drug and Cosmetic Act, the applicant certifies that the applicant did not and will not use in any capacity, in connection with this application, the services of any person listed pursuant to section 306(e) as debarred under subsections 306(a) or (b) of the Act.

Catherine L. Clark, Director, US Regulatory Affairs

Project Manager Overview of NDA 20-297/S-009
Coreg (carvedilol) 3.125, 6.25, 12.5 and 25 mg Tablets
GlaxoSmithKline
Related IND[redacted]

Background:

Coreg is currently approved for the treatment of hypertension and mild to severe heart failure. S-009 submitted September 27, 2002, contains one major study (CAPRICORN) which evaluated the safety and efficacy of carvedilol in patients with recent myocardial infarction and left ventricular function who were receiving appropriate treatments for the immediate and long-term management of post-infarction patients.

Meetings held:

Pre-Advisory Committee- November 7, 2002
December 13, 2002

Medical/Statistical Review:

In a joint review dated December 2, 2002, Dr. Stockbridge and Dr. Hung, several issues were noted that resulted in Coreg being discussed at the Advisory Committee Meeting held January 7, 2003. No recommendation was made in the review about approvablility.

In an amendment dated December 9, 2002 (Dr. Hung) and December 10, 2002 (Dr. Stockbridge), Table 10 was replaced from the original review. This consisted of minor changes in the table to reflect patients who were hospitalized and died on the same day and did not change the reviewer's conclusions.

In an amendment dated December 17, 2002, Dr. Hung and Dr. Stockbridge stated they found no compelling internal inconsistencies in the mortality data of CAPRICORN as was stated in the original review.

Peds Rule- Pediatric studies were waived for this indication, as there are too few children with the disease to study. Currently a study entitled "A Multicenter, Placebo-Controlled, 8-Month Study of the Effect of Twice Daily Carvedilol in Children with Congestive Heart Failure Due to Systemic Ventricular Systolic Dysfunction" is ongoing under IND[redacted] A Pediatric Written Request was issued on October 3, 2000.

Advisory Committee Meeting:

On January 7, 2003, the Advisory Committee Meeting discussed Coreg. The committee voted 11 (Yes)-0 (No) on the following question, Should carvedilol be indicated to reduce mortality in patients with left ventricular dysfunction after myocardial infarction. In addition the committee voted 0 (Yes)- 11 (No) on the following question, The Sponsor also seeks a claim for reduction in recurrent MI, based on the observation of 45 adjudicated events on placebo and 27 on carvedilol (of which 16 and 12 were fatal). Do these data support a claim?

DDMAC Review:

In a review dated March 17, 2003, Andrew Haffer submitted comments based on the draft labeling submitted from the sponsor dated March 6, 2003.

RHPM Summary

No Biopharmaceutical, Pharmacology, Chemistry, or Microbiology reviews were included in this supplement, as they were deemed not necessary for approval.

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/s/

Melissa Robb
3/27/03 01:05:24 PM
CSO

********** -COMM. JOURNAL- ********** DATE MAR-27-2003 ***** TIME 14:39 ********

MODE = MEMORY TRANSMISSION START=MAR-27 14:29 END=MAR-27 14:39

FILE NO.=955

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	a	74576	027/027	00:09:09

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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Rockville, MD 20857

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1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	7-4576
Attention:	FOI
Company Name:	
Phone:	
Subject:	AP Letter and Draft Labeling
Date:	3/27/03
Pages including this sheet:	28

From: Melissa Robb
Phone: 301-594-5313
Fax: 301-594-5494

PLEASE LET ME KNOW YOU RECEIVED THIS. THANK YOU.

********** -COMM. JOURNAL- ********** DATE MAR-27-2003 ***** TIME 12:52 *********

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FILE NO.=952

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	#	912157514926	004/004	00:00:53

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Transmitted to FAX Number:	215-751-4926
Attention:	**Ms. Catherine Clark**
Company Name:	**SKB**
Phone:	215-751-4112
Subject:	**Action Letter NDA 20-297/S-009**
Date:	3/27/03
Pages including this sheet:	4
From:	**Melissa Robb**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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From:	**Melissa Robb**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 20-297	Efficacy Supplement Type SE-1	Supplement Number S-009
Drug: Coreg (carvedilol)	Applicant: GlaxoSmithKline	
RPM: Melissa Robb	HFD-110	Phone # 301-594-5313
Application Type: (X) 505(b)(1) ( ) 505(b)(2)	Reference Listed Drug (NDA #, Drug name):	

❖ Application Classifications:	
• Review priority	( ) Standard (X) Priority
• Chem class (NDAs only)	N/A
• Other (e.g., orphan, OTC)	N/A
❖ User Fee Goal Dates	March 27, 2003
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review
❖ User Fee Information	
• User Fee	(X) Paid
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) ( ) Other
❖ Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No
• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	N/A
• OC clearance for approval	N/A
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification and certifications from foreign applicants are co-signed by U.S. agent.	(X) Verified
❖ Patent	
• Information: Verify that patent information was submitted	(X) Verified
• Patent certification [505(b)(2) applications]: Verify type of certifications submitted	N/A 21 CFR 314.50(i)(1)(*i*)(A) ( ) I ( ) II ( ) III ( ) IV 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• For paragraph IV certification, verify that the applicant notified the patent holder(s) of their certification that the patent(s) is invalid, unenforceable, or will not be infringed (certification of notification and documentation of receipt of notice).	N/A ( ) Verified
❖ Exclusivity Summary (approvals only)	X

❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	X
[redacted]	
❖ Actions	[redacted]
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	N/A
• Status of advertising (approvals only)	(X) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	[redacted]
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None ( ) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable)	[redacted]
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	X
• Original applicant-proposed labeling	X
• Labeling reviews (including DDMAC, Office of Drug Safety trade name review, nomenclature reviews) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	X-DDMAC
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	N/A
❖ Labels (immediate container & carton labels)	[redacted]
• Division proposed (only if generated after latest applicant submission)	N/A
• Applicant proposed	N/A
• Reviews	N/A
❖ Post-marketing commitments	[redacted]
• Agency request for post-marketing commitments	N/A
• Documentation of discussions and/or agreements relating to post-marketing commitments	N/A
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	X
❖ Memoranda and Telecons	X
❖ Minutes of Meetings	[redacted]
• EOP2 meeting (indicate date)	N/A
• Pre-NDA meeting (indicate date)	N/A
• Pre-Approval Safety Conference (indicate date; approvals only)	N/A
• Other- Pre Advisory Committee Meetings	November 7, 2002 December 13, 2002
❖ Advisory Committee Meeting	[redacted]
• Date of Meeting	January 7, 2003
• 48-hour alert	N/A
❖ Federal Register Notices, DESI documents, NAS, NRC (if any are applicable)	X

Clinical and Statistical Information	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	N/A
❖ Clinical review(s) *(indicate date for each review)*	March 27, 2003 December 17, 2002 December 10, 2002 December 2, 2002
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	N/A
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	N/A
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	X
❖ Statistical review(s) *(indicate date for each review)*	December 17, 2002 December 9, 2002 December 2, 2002
❖ Biopharmaceutical review(s) *(indicate date for each review)*	N/A
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	N/A
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	N/A
• Bioequivalence studies	N/A
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	March 26, 2003
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	March 26, 2003
• Review & FONSI *(indicate date of review)*	N/A
• Review & Environmental Impact Statement *(indicate date of each review)*	N/A
❖ Micro (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	N/A
❖ Facilities inspection (provide EER report)	Date completed: N/A ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	N/A ( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical (Pharm/Tox) Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	N/A
❖ Nonclinical inspection review summary	N/A
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	N/A
❖ CAC/ECAC report	N/A

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/s/

Melissa Robb
3/27/03 12:47:16 PM

NDA REGULATORY FILING REVIEW
(Includes Filing Meeting Minutes)

NDA Number: NDA 20-297/S-009
Name: Coreg (carvedilol) 3.125mg, 6.25mg, 12.5mg and 25mg Tablets
Supplement Type: SE1

Applicant: SmithKline Beecham Corporation d/b/a GlaxoSmithKline

Date of Application: September 27, 2002
Date of Receipt: September 27, 2002
Date of Filing Meeting: November 21, 2002
Filing Date: November 26, 2002

Indication(s) requested: To reduce mortality and the risk of infarction in clinically stable patients who have survived the acute phase of myocardial infarction.

Type of Application: Full NDA _____ Supplement ___X_____
(b)(1) _____X_____ (b)(2) _____
[If the Original NDA of the supplement was a (b)(2), all subsequent supplements are (b)(2)s; if the Original NDA was a (b)(1), the supplement can be either a (b)(1) or (b)(2)]

If you believe the application is a 505(b)(2) application, see the 505(b)(2) requirements at the end of this summary.

Therapeutic Classification: S_____ P____X_____
Resubmission after a withdrawal or refuse to file __N/A_____
Chemical Classification: (1,2,3 etc.)_____
Other (orphan, OTC, etc.)___N/A_____

Has orphan drug exclusivity been granted to another drug for the same indication? N/A

If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?
N/A

If the application is affected by the application integrity policy (AIP), explain. No

User Fee Status: Paid _____X_____ Waived (e.g., small business, public health) ____N/A____
Exempt (orphan, government) ____N/A_____
Form 3397 (User Fee Cover Sheet) submitted: YES_____X__ NO_____
User Fee ID#_____4347_____
Clinical data? YES____X___ NO _____ Referenced to NDA# _____
Date clock started after UN _____N/A_____

User Fee Goal date: ____March 26, 2003_____

Action Goal Date (optional) _____N/A_____

- Does the submission contain an accurate comprehensive index? YES
- Form 356h included with authorized signature? YES

If foreign applicant, the U.S. Agent must countersign.

- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:

- If electronic NDA, does it follow the Guidance? YES
  If an electronic NDA: all certifications must be in paper and require a signature.

- If Common Techinical Document, does it follow the guidance? N/A

- Patent information included with authorized signature? YES

- Exclusivity requested? NO

Note: An applicant can receive exclusivity without requesting it, therefore, requesting exclusivity is not a requirement.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, the U.S. Agent must countersign.

  Debarment Certification must have correct wording, e.g.: "I, the undersigned, hereby certify that _____ Co. did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug and Cosmetic Act in connection with the studies listed in Appendix ____." Applicant may not use wording such as, " To the best of my knowledge, ..."

- Financial Disclosure included with authorized signature? YES
  (Forms 3454 and/or 3455)
  If foreign applicant, the U.S. Agent must countersign.

- Has the applicant complied with the Pediatric Rule for all ages and indications? Study ongoing on pediatric patients with CHF, IND [redacted] by Dr. Robert E. Shaddy

- Field Copy Certification (that it is a true copy of the CMC technical section)? N A

Refer to 21 CFR 314.101(d) for Filing Requirements

PDUFA and Action Goal dates correct in COMIS? YES
If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.

Drug name/Applicant name correct in COMIS? YES
If not, have the Document Room make the corrections.

List referenced IND numbers: [redacted]

End-of-Phase 2 Meeting? Date_____ NO
If yes, distribute minutes before filing meeting.

Pre-NDA Meeting(s)? Date(s)_____ NO
If yes, distribute minutes before filing meeting.

Project Management

Copy of the labeling (PI) sent to DDMAC? YES

Trade name (include labeling and labels) consulted to ODS/Div. of Medication Errors and Technical Support? N/A

MedGuide and/or PPI consulted to ODS/Div. of Surveillance, Research and Communication Support? N/A

OTC label comprehension studies, PI & PPI consulted to ODS/ Div. of Surveillance, Research and Communication Support? N/A

Advisory Committee Meeting needed? YES, date if known __1/7/03_____

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did sponsor request categorical exclusion for environmental assessment? YES
  If no, did sponsor submit a complete environmental assessment? N/A
  If EA submitted, consulted to Nancy Sager (HFD-357)? N/A
- Establishment Evaluation Request (EER) package submitted? N/A
- Parenteral Applications Consulted to Sterile Products (HFD-805)? N/A

If 505(b)(2), complete the following:

Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").

Name of listed drug(s) and NDA/ANDA #:

Is the application for a duplicate of a listed drug and eligible for approval under section 505(j)? (Normally, FDA will refuse-to-file such applications.)
YES NO

Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)?
If yes, the application must be refused for filing under 314.54(b)(1) YES NO

Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD?
YES NO

If yes, the application must be refused for filing under 314.54(b)(2)

Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

____ 21 CFR 314.50(i)(1)(i)(A)(2): The patent has expired.

____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

If filed, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314.52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314.52(e)].

____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): Information that is submitted under section 505(b) or (c) of the act and 21 CFR 314.53 is for a method of use patent, and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent.

____ 21 CFR 314.54(a)(1)(iv): The applicant is seeking approval only for a new indication and not for the indication(s) approved for the listed drug(s) on which the applicant relies.

Did the applicant:

- Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

  YES NO

- Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

  YES NO

- Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

  YES NO

Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

YES NO

ATTACHMENT

MEMO OF FILING MEETING

DATE: November 21, 2002

BACKGROUND

This is a supplement to an already approved NDA for the use of Coreg for the treatment of hypertension and mild to severe heart failure. This supplement provides data in support of a new proposed indication:

> "*Coreg* is indicated to reduce mortality and the risk of infarction in clinically stable patients who have survived the acute phase of a myocardial infarction and have a left ventricular ejection fraction of < 40%.
>
> *Coreg* may be used in patients who are, or are not receiving ACE inhibitors, digitalis, diuretics or nitrate therapy. *Coreg* may be used in conjunction with established treatments for acute myocardial infarction such as thrombolytics, intravenous beta-blockers, anti-platelet therapy, and lipid lowering agents."

ATTENDEES:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Team Leader, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Kasturi Srinivasachar, Ph.D.	Team Leader, Chemistry, HFD-110
Ramsharan Mittal, Ph.D.	Chemist, HFD-110
James Willard, Ph.D.	Pharmacologist, HFD-110
Lydia Velazquez, Pharm.D.	Pharmacokineticist, HFD-860
Robert Shibuya, Ph.D.	Division of Scientific Investigations
Zelda McDonald	Chief Regulatory Health Project Manager, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

ASSIGNED REVIEWERS:

Discipline	**Reviewer**	
Medical:	Norman Stockbridge, M.D., Ph.D.	January 1, 2003
Statistical:	James Hung, Ph.D.	January 1, 2003
Chemist:	Ramsharan Mittal, Ph.D.	
Pharmacology:	James Willard, Ph.D.	
Biopharmaceutical:	Lydia Velazquez, Pharm.D.	
Project Manager:	Melissa Robb	

Per reviewers, all parts in English, or English translation? YES__X__ NO___

CLINICAL – File ____X_____ Refuse to file _____

- Clinical site inspection needed: YES_____ NO____X____

MICROBIOLOGY CLINICAL – File____N/A_____ Refuse to file_____

STATISTICAL – File _____X_____ Refuse to file _____

BIOPHARMACEUTICS – File ____N/A_____ Refuse to file _____

- Biopharm. inspection Needed: YES_____ NO ___X_____

PHARMACOLOGY – File _____X_____ Refuse to file _____

CHEMISTRY –

- Establishment(s) ready for inspection? N/A File___X__ Refuse to file _____

REGULATORY CONCLUSIONS/DEFICIENCIES:

___X____The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

_____ The application is unsuitable for filing. Explain why:

/S/

_____
Melissa Robb
Regulatory Project Manager, HFD-110

Drafted: 11/22/02 Finaled: 11/26/02

RD:
Throckmorton 11/25/02
Stockbridge 11/25/02
Hung 11/22/02
Srinivasachar 11/22/02
Mittal 11/22/02
Willard 11/22/02
Velaquez 11/22/02
Shibuya 11/22/02
McDonald 11/25/02

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/s/

Melissa Robb
11/26/02 12:57:05 PM
Filing Meeting Minutes Attached, Reviewed by Dr. Throckmorton 11/25/02

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Rockville, MD 20852

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Attention:	**Ms. Catherine Clark**
Company Name:	**SKB**
Phone:	215-751-4112
Subject:	**Meeting Confirmation**
Date:	1/27/03
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From:	**Melissa Robb**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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Confirmation of Meeting

Drug:	Carvedilol Controlled Release
NDA:	20-297
Sponsor:	SmithKline Beecham
Date Requested:	July 25, 2002
Date Confirmation Faxed:	August 2, 2002
Rescheduled per SKB:	August 28, 2002
Date Confirmation of reschedule faxed:	September 3, 2002
Rescheduled per FDA:	September 24, 2002
Date Confirmation of reschedule faxed:	September 26, 2002
Reschedule per SKB:	November 14, 2002
Date Confirmation of reschedule faxed:	November 18, 2002
Reschedule per SKB:	November 19, 2002
Date Confirmation of reschedule faxed:	November 20, 2002
Rescheduled per SKB:	January 23, 2003
Date Confirmation of reschedule faxed:	January 27, 2003

Type:	Pre-NDA
Classification:	B

Meeting Date:	March 25, 2003
Meeting Time:	11:00 am
Location:	Conference Room "F," Fifth Floor, Woodmont Office Complex 2 1451 Rockville Pike, Rockville MD

FDA Participants:

Robert Temple, M.D.	Director, ODE I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Team Leader, HFD-110
Albert DeFelice, Ph.D.	Team Leader, Pharmacology, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Kasturi Srinivasachar, Ph.D.	Chemistry Team Leader, HFD-810
Patrick Marroum, Ph.D.	Team Leader, Biopharmaceutics, HFD-860
Robert Shibuya, M.D.	Division of Scientific Investigations
Salma Koessel, M.D.	Medical Officer, HFD-110
Mehul Desai, M.D.	Medical Officer, HFD-110
Zelda McDonald	Chief, Regulatory Health Project Manager, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

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Confirmation of Teleconference

Drug:	Coreg (carvedilol) Tablets
IND:	[redacted]
Sponsor:	GlaxoSmithKline
Date Requested:	January 15, 2003
Date Confirmation Faxed:	January 22, 2003
Type:	Safety/Guidance
Classification:	C
Teleconference Date:	February 11, 2003
Teleconference Time:	11:00 am

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Deputy Director, Division of Cardio-Renal Drug Products, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

Confirmation of Meeting

Drug:	Carvedilol
NDA:	20-297/S-009
Sponsor:	SmithKline Beecham
Date Requested:	January 24, 2003
Date Confirmation Faxed:	January 27, 2003
Type:	Labeling
Classification:	C
Meeting Date:	February 13, 2003
Meeting Time:	9:00 am
Location:	Conference Room "F," Fifth Floor, Woodmont Office Complex 2 1451 Rockville Pike, Rockville MD

FDA Participants:

Robert Temple, M.D.	Director, ODE I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Team Leader, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Melissa Robb	Regulatory Health Project Manager, HFD-110

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/s/

Melissa Robb
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CSO

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MODE = MEMORY TRANSMISSION START=NOV-18 10:38 END=NOV-18 10:39

FILE NO.=591

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1451 Rockville Pike
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Company Name:	**SKB**
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Confirmation of Meeting

Drug:	Coreg (carvedilol) Tablets
NDA:	20-297
Sponsor:	GlaxoSmithKline
Date Requested:	November 14, 2002
Date Confirmation Faxed:	November 18, 2002
Type:	Other, Pre-Advisory Committee Meeting
Classification:	C
Meeting Date:	Decmeber 13, 2002
Meeting Time:	1:00 pm
Location:	Conference Room "F," Fifth Floor, Woodmont Office Complex 2 1451 Rockville Pike, Rockville MD

FDA Participants:

Robert Temple, M.D.	Director, ODE I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Medical Team Leader, HFD-110
James Hung. Ph.D.	Team Leader, Statistics, HFD-710
Jayne Peterson, R.Ph., J.D.	Supervisory Health Science Administrator
Zelda McDonald	Chief, Regulatory Health Project Manager, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

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001	OK	a	912157514926	004/004	00:01:16

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Meeting Minutes
December 13, 2002

NDA#	20-297/S-009
Drug:	Coreg (carvedilol) Tablets
Sponsor:	GlaxoSmithKline
Subject:	January 7, 2003 Advisory Committee Meeting for CAPICORN study

FDA Participants:

Robert Temple, M.D.	Director, ODE-I, HFD-101
Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
James Hung, Ph.D.	Team Leader, Statistics, HFD-710
Jayne E. Peterson, R.Ph., J.D.	Supervisory Health Science Administrator
Dornette D. Spell Lesane	Health Science Administrator
Melissa Robb	Regulatory Health Project Manager, HFD-110

GlaxoSmithKline Participants:

Catherine K. Clark	Director, NA Regulatory Affairs
Mary Ann Lukas, M.D.	Senior Director, Cardiovascular Therapeutic Area
Rosemary Oakes	Associate Director, Statistics and Programming
Milton Packer, M.D.	Consultant, Dickinson W. Richards Professor of Medicine Chief, Division of Circulatory Physiology, Columbia University College of Physicians and Surgeons
Clare Kahn, Ph.D.	Vice President, Cardiovascular, Metabolic and Genitourinary, US Regulatory Affairs
Terry L Holcslaw, Ph.D.	Director, Cardiovascular/Urology Therapeutic Area, Clinical Development
Rozsa Schlenker-Herceg, M.D.	Director Clinical Development, Cardiovascular Therapeutic Area, Clinical Development & Medical Affairs
Placido B Grino, M.D., F.A.C.P.	Vice President, Cardiovascular/ Urology Therapy Area Head, Clinical Development & Medical Affairs
Névine Zariffa, Mmath	Therapy Area Director, Cardiovascular and Metabolism, Biomedical Data Sciences
Bruce D. Jensen, Ph.D.	Director, Cardiovascular and Urology, Project Team Leadership and Management
Professor Ian Ford	Consultant, Director, Robertson Centre of Biostatistics, University of Glasgow

Background:

GlaxoSmithKline submitted a supplement to NDA 20-297 on September 27, 2002 containing one major study (CAPRICORN) that was conducted in accordance with Protocol SK&F 105517/269 entitled "A multinational.

multicenter, randomized, double-blind, parallel group study to determine the effects of carvedilol on mortality and morbidity in patients with left ventricular dysfunction, with or without clinical evidence of heart failure, post myocardial infarction". The protocol was initially submitted to the Division under IND [redacted] on June 3, 1997 (Serial 524) and last amended in a submission on August 16, 1999 (Serial 620).

The trial evaluated the safety and efficacy of carvedilol in patients with a recent myocardial infarction (<21 days) and left ventricular dysfunction, who were receiving all appropriate treatments for the immediate and long-term management of post-infarction patients. Data were collected regarding fatal and non-fatal events whether or not patients continued receiving their study medications.

The original primary endpoint of the CAPRICORN trial was all-cause mortality. A protocol amendment was submitted on July 27, 1999 that changed the primary endpoints to all-cause mortality or cardiovascular hospitalization and all-cause mortality. The focus was on the first parameter as evidenced by the alpha spending. The significance level for all-cause mortality and cardiovascular hospitalization was set to 4.5%, whereas the alpha level for the endpoint all-cause mortality was set to 0.5%.

The Division of Cardio-Renal Drug Products has placed the CAPRICORN trial on the Cardiovascular and Renal Drugs Advisory Committee Meeting (ACM) Agenda for January 7, 2003 due to the difficulty interpreting the mortality results. During a teleconference with GlaxoSmithKline on November 7, 2002, the Division of Cardio-Renal Drugs had offered to meet with GSK prior to the ACM.

Meeting:

The Agency began the meeting by informing GSK that draft questions for the ACM are being worked on by the Division and will be available to them by the early part of next week. The Agency believes a major focus of the meeting will be the question of when can you learn something you did not plan on learning.

GSK asked who the consultants would be at the ACM and their disciplines. The Agency stated they can not give out names until the list is finalized. The list may not be final until shortly prior to the ACM. The Division was able to share that the potential consultants are cardiologists.

The first issue GSK wished to discuss was Table 10 in the review written by Dr. Stockbridge and Dr. Hung, titled Time to event for death or cardiovascular hospitalization. GSK believed this table was an inaccurate depiction of the data since it only incorporated those patients with an event. They did not agree with the reviewers' assertion that the data gathered from the trial are inconsistent. Dr. Hung pointed out this table is meant to be descriptive only and was not to be used for an analysis, as no p-values were assigned. GSK acknowledged this fact, but believes that it does not account for the whole picture of the study. GSK also asserted that this "minor" issue might distract the Advisory Committee from the main issue at hand, finding vs. discovery. The Agency stated that further internal discussion would be needed on this point.

GSK also inquired about a paragraph written in the Conclusion of the above-mentioned review. It is stated that "the Agency has acted as if studies all implicitly have alpha=0.05 for mortality, independent of the primary end point." GSK wanted specific cases in which this policy had been used. The Agency identified experience with Flolan, Valsartan, and carvedilol as illustrations. The Agency pointed out that this is a relatively new issue; in the past where there was only a single mortality finding, there tended to be extreme p-values (e.g. beta blockers post-reinfarction trials, thrombolysis trials, CONSENSUS). The Agency also noted that a mortality finding with a p-value less than 0.05 even if not anticipated, would make it difficult to randomize patients to further placebo-controlled trials. So the difficult question is what to do with a nominally significant finding that did not involve the planned endpoint of the trial. GSK believes that the mortality finding, with a p-value of 0.031, coupled with confirmation of available evidence on carvedilol and perhaps other beta blockers in both heart failure and left

ventricular systolic function in post-MI patients both recent and remote, is convincing. The Agency pointed out this is why they are on the agenda for the ACM.

Signature, minutes preparer: /S/

Concurrence Chair: /S/

Drafted: 12/13/02 Finaled: 1/9/03

RD:

Temple	1/8/03
Throckmorton	1/3/03
Stockbridge	1/3/03
Hung	1/2/03
Peterson	1/2/03
Spell Lesane	12/13/02

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
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Company Name:	**SKB**
Phone:	215-751-4112
Subject:	**Teleconference Meeting Minutes 11/7/02**
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From:	**Melissa Robb**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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Teleconference Minutes
November 7, 2002

NDA#	20-297/S-009
Drug:	Coreg (carvedilol) Tablets
Sponsor:	GlaxoSmithKline
Subject:	January 7, 2003 Advisory Committee Meeting for CAPICORN study

FDA Participants:

Douglas C. Throckmorton, M.D.	Director, Division of Cardio-Renal Drug Products, HFD-110
Norman Stockbridge, M.D., Ph.D.	Team Leader, Medical, HFD-110
Jayne E. Peterson, R.Ph., J.D.	Supervisory Health Science Administrator
Zelda McDonald	Chief Regulatory Health Project Manager, HFD-110
Melissa Robb	Regulatory Health Project Manager, HFD-110

GlaxoSmithKline Participants:

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Mary Ann Lukas, M.D.	Senior Director, Cardiovascular Therapeutic Area
Rosemary Oakes	Associate Director, Statistics and Programming
Milton Packer, M.D.	Consultant, Dickinson W. Richards Professor of Medicine

Background:

GlaxoSmithKline submitted a supplement to NDA 20-297 on September 27, 2002 containing one major study (CAPRICORN) that was conducted in accordance with Protocol SK&F 105517/269 entitled "A multinational, multicenter, randomized, double-blind, parallel group study to determine the effects of carvedilol on mortality and morbidity in patients with left ventricular dysfunction, with or without clinical evidence of heart failure, post myocardial infarction". The protocol was initially submitted to the Division under IND [redacted] on June 3, 1997 (Serial 524) and last amended in a submission on August 16. 1999 (Serial 620).

The trial evaluated the safety and efficacy of carvedilol in patients with a recent myocardial infarction (<21 days) and left ventricular dysfunction, who were receiving all appropriate treatments for the immediate and long-term management of post-infarction patients. Data were collected regarding fatal and non-fatal events whether or not patients continued receiving their study medications.

The original primary endpoint of the CAPRICORN trial was all-cause mortality. A protocol amendment was submitted on July 27, 1999 that changed the primary endpoints to all-cause mortality or cardiovascular hospitalization and all-cause mortality. The focus was on the first parameter as evidenced by the alpha spending. The significance level for all-cause mortality and cardiovascular hospitalization was set to 4.5%, whereas the alpha level for the endpoint all-cause mortality was set to 0.5%.

The Division of Cardio-Renal Drug Products had informed GlaxoSmithKline that they planned for CAPRICORN to be on the Cardiovascular and Renal Drugs Advisory Committee Meeting (ACM) Agenda for January 7, 2003 due to the difficulty interpreting the mortality results. GlaxoSmithKline requested a teleconference with the Division to persuade them that the ACM was not needed for carvedilol.

Teleconference:

GlaxoSmithKline asked the Division why they believed that CAPRICORN needed to go to the ACM. The Division would like the Advisory Committee's opinion on whether studies have two chances to win- the primary endpoint and mortality- and whether it matters if the results do not support the primary hypothesis.

GlaxoSmithKline agreed that it was an interesting case, but felt that the issue was transparent. They believe they have provided meaningful statistics illustrating that carvedilol decreases mortality by 23%.

The Division asked GlaxoSmithKline why they are so reluctant to go to the ACM. GlaxoSmithKline stated that the ACM requires a great deal of work. In addition, they feel that CAPRICORN results are consistent with what is known about the drug and the disease. They also believe that the population of the CAPRICORN trial was in the first phase of heart failure and therefore, the results were not surprising.

GlaxoSmithKline asked what the Division planned to gain by participating in the ACM. The Division stated they had three specific concerns. First, the Division does not believe the interpretation of the data is transparent as GlaxoSmithKline describes it. Second, the Division would be requesting guidance on how to describe the findings in labeling, if the results were to be found credible. Finally, this is an opportunity to discuss this issue with the community as a whole, in an open forum.

GlaxoSmithKline wanted to know if any additional issues were present, besides that of not meeting the stated primary endpoint. The Division stated this is the only issue to date. GlaxoSmithKline also inquired as to when reviews would be available. Dr. Stockbridge stated that he has been working on his review, but knows that Dr. Hung, Statistician, has not yet begun. He stated he would be able to get some information to GlaxoSmithKline as soon as Dr. Hung had done some sort to review and analysis. This would not be a review, as he is not able to state any conclusions on data due to the Freedom of Information Act. The Division would only be able to provide data analysis and data tables. In addition, Dr. Stockbridge stated he is not trying to hide any issues from GlaxoSmithKline.

Conclusion

The CAPRICORN study will become part of the agenda on the January 7, 2003 ACM Agenda. Ms. Catherine Clark will contact Ms. Melissa Robb with any further questions regarding information required for ACM. Ms. Jayne Peterson stated she will send a letter with instructions to Ms. Clark. In addition, she stated that a fully releasable background package would be due to her office by December 3, 2002 as the deadline has already passed for materials that are exempt from disclosure. Finally, Dr. Throckmorton offered to meet with GlaxoSmithKline prior to the ACM to discuss any issues or concerns. Ms. Clark plans to schedule this meeting with Ms. Robb.

Signature, minutes preparer: /S/

Concurrence Chair: /S/ 11/20/02

Drafted: 11/13/02 Finaled: 11/18/02

RD:

Throckmorton	11/15/02
Stockbridge	11/13/02
Peterson	11/13/02
McDonald	11/14/02

********** -COMM. JOURNAL- ********** DATE NOV-20-2002 ***** TIME 15:47 **********

MODE = MEMORY TRANSMISSION START=NOV-20 15:45 END=NOV-20 15:47

FILE NO.=647

STN NO.	COMM.	ONE-TOUCH/ ABBR NO.	STATION NAME/TEL NO.	PAGES	DURATION
001	OK	8	912157514926	003/003	00:01:07

-FDA,CDER,OND,ODEI,DCRDP -

********** -CARDIO RENAL - ***** - 301 594 5494- **********

DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

US Mail address:
FDA/CDER/HFD-110
5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number:	215-751-4926
Attention:	**Ms. Catherine Clark**
Company Name:	**SKB**
Phone:	215-751-4112
Subject:	**Teleconference Meeting Minutes 11/7/02**
Date:	11/20/02
Pages including this sheet:	2
From:	**Melissa Robb**
Phone:	**301-594-5313**
Fax:	**301-594-5494**

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Item 19 Financial Disclosure

Catherine K. Clark

U.S. Regulatory Affairs

GSK Document Number: SKF-105517/RSD-101T3B/1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Item 8A.1 for List of Investigators	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
David E. Wheadon, M.D.	Senior Vice President, US Regulatory Affairs
FIRM/ORGANIZATION: SmithKline Beecham Corporation d/b/a GlaxoSmithKline	
SIGNATURE: David E Wheadon, MD	DATE: September 30, 2002

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Regarding all investigators participating in Study 269 (see Item 8A.1 for List of Investigators), there was 1) no financial arrangement with any investigator whereby the value of the compensation to the investigator could be affected by the outcome of the study and 2) no investigator was the recipient of significant payments as defined in 21 CFR 54.2(f).

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Item 18 User Fee Cover Sheet

Catherine K Clark

U.S. Regulatory Affairs

GSK Document Number: SKF-1055517/RSD-101T39/1

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved: OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1. APPLICANT'S NAME AND ADDRESS

SmithKline Beecham Corporation d/b/a GlaxoSmithKline
One Franklin Plaza
P.O. Box 7929
Philadelphia, PA 19101

2. TELEPHONE NUMBER *(Include Area Code)*

(610) 917-5368

3. PRODUCT NAME

Coreg® brand of carvedilol tablets

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

NDA 20-297

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☑ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS "YES", CHECK THE APPROPRIATE RESPONSE BELOW:

☑ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☐ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

_____
(APPLICATION NO. CONTAINING THE DATA).

6. USER FEE I.D. NUMBER

4347

7. IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See Item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See Item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See Item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION? ☐ YES ☑ NO

(See Item 8, reverse side if answered YES)

Public reporting burden for this collection of information is estimated to average 30 minutes per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CBER, HFM-99
1401 Rockville Pike
Rockville, MD 20852-1448

and

Food and Drug Administration
CDER, HFD-94
12420 Parklawn Drive, Room 3046
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Catherine K. Clark	Catherine K. Clark Director, U.S. Regulatory Affairs	September 30, 2002

FORM FDA 3397 (4/01)

Created by: PSC Media Arts (301) 443-2454 EF

Robb, Melissa

From: Catherine.K.Clark@gsk.com
Sent: Monday, November 25, 2002 3:05 PM
To: RobbM@cder.fda.gov
Cc: RAID@gsk.com
Subject: NDA 20-297 (S-009) - Categorical Exclusion for Environmental Assessment

Dear Melissa:
Attached in accordance with your request is the subject document.

All the best,

Catherine